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The Natural Polymer Encapsulated Novel Nanoformulation of Simvastatin for the Treatment of Hyperlipidemia

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Summary

Maintaining good health and preventing diseases are the most important factors for a person's quality of life. In developed and developing countries alike, health concerns are serious economic and social challenges. Preventable communicable or infectious diseases like malaria and HIV/AIDS account for millions of death in world every year especially in low-income countries [1]. Non-communicable or chronic diseases like heart disease and diabetes are increasing across the globe. Between communicable and non-communicable diseases (NCD), non-communicable diseases are leading cause of death. In India, total death by NCD was estimated as 60% (981,600) during 2015. Among various NCD, death due to cardiovascular disease (CVD) was calculated to be higher (26%) compared to other NCD (cancer - 7%, respiratory disease - 13%, and diabetes - 2%). CVD is a chronic process that begins during adolescence and aggravated by risk factors such as family history of CVD, diabetes, hypertension, hyperlipidemia, obesity, life style, etc., [2,3] in which hyperlipidemia, the second most risk factor for CVD (first one is hypertension), was taken for this research proposal.

One essential condition for good health and to rectify the above-said defect is maintaining proper levels of circulating blood fats, cholesterol, and triglycerides. In nature, the body is able to regulate the production and removal of the lipoproteins in our system so as to keep them at healthy levels. Conversely, if these levels have become too high for the body to control, then it is important to lower both dietary cholesterol as well as cholesterol produced by liver by artificial mode of drug delivery applications [4-7].

Most of the total cholesterol found in the body is of endogenous origin. The liver is the foremost site of cholesterol biosynthesis. This is the foremost reason of the progress of hyperlipidemia. Thus, the selective inhibition of HMG-CoA reductase in the liver is a significant step in *de novo* synthesis of cholesterol. The lipid-lowering agents of choice are the statins, which are generally considered safe and effective [8]. Statin drugs can reduce the endogenous synthesis of cholesterol (lipids) and prevent the onset and development of atherosclerosis and are therefore used as an effective treatment against hyperlipidemia and primary hypercholesterolemia [9]. Statin works in the liver to control cholesterol and lowers LDL or "bad" cholesterol and raises the level of HDL or "good" cholesterol.

The safety profile becomes a predominantly significant problem when aggressive treatment is under concern. In general, statins have an excellent safety record, but serious adverse effects with statin therapy are observed in the liver and skeletal muscle like myopathy and elevated hepatotoxicity, particularly at higher doses [10,11]. After administration, the bioavailability and the general circulation of statin drugs are fairly low due to the first-pass metabolism in the liver and clearance by the digestive system and do not accomplish control of dietary cholesterol.

Simvastatin is a prodrug, it has low bioavailability (5%), extensive protein binding (95%), and elimination half-life of 2 hours. Thus, in order to overcome the poor bioavailability of this drug, a higher dose is used which leads to severe side effects.

If above demerits are bypassed, then simvastatin will be the better candidate which meets the therapeutic needs of patients while eliciting fewer adverse effects and presenting better pharmacological effects.

Inability to produce expected pharmacological action is not due to the drug candidate but may be due to obstacles of that drug to reach the target site and reaching non-target sites too. Finding new drug entities and introducing them to the market takes several years. Optimizing the problem of existing drug molecules and introducing a new drug delivery system would be beneficial for these obstacles. So, reverse engineering is best for this problem.

Nothing can substitute naturally occurring resources used for health benefits since they have minimum side effects, which is in contrary to existing synthetic drugs with maximum side effects [12]. Identification of active principles and their molecular targets from

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traditional medicine will have enormous opportunities for modern drug development. So, the formulation consisting of a combination of synthetic and natural agents would have beneficial effects in reducing toxicity and increasing therapeutic index. Some natural polymers viz almond gum, guar gum, guggul lipid, and chitosan are reported to have antihyperlipidemic action of their own [13-16]. So, if these polymers are used to encapsulate the drug statin, it might synergize the action and release the drug in a controlled manner. If natural polymers exhibiting antihyperlipidemic action are used, only a very less quantity of statin drug is required for formulation. So, severe side effects caused by high statin doses might be reduced.

Our studies had the objective of formulating novel nanoformulation of simvastatin encapsulated with chitosan polymer. The study reports explored the increase in solubility, bioavailability, and reduction in dose, muscle toxicity, PG efflux mechanism. The positive results obtained were due to synergistic effect of chitosan polymer and its bile binding capacity enhanced anti-hyperlipidemic activity of simvastatin in nanoformulation. The results obtained after *in vitro* and preclinical evaluation encourages the future scope of clinical trials.

The prepared reconstituted nanoformulation can be further formulated into either tablet, capsules, suspension or oral liquids etc. Moreover this strategy can be used for other candidates of HMG-COA reductase inhibitors like pravastatin, lovastatin, rosuvastatin etc

Conclusion

Though the modern medicine helps to maintain acute and chronic diseases, the long-term usage leads to severe side effects. The time to manage and cure of particular disease with aid of natural substances exhibiting therapeutic effects alone requires specific duration. Therefore, use of dosage forms consisting of both low dose API and natural gum or substances positively helps to manage and cure diseases in short duration without negligible side effects which was proved by our research.

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